Remarks

Claims 1-18 remain in the present application. Claims 1-9 have been withdrawn from consideration based on a restriction requirement. Claims 10-18 remain under consideration and claims 19-27 have been added. The Office Action, dated April 24, 2002, has been carefully considered. In Response to the Office Action, please consider the following remarks.

The claims have been amended to more clearly set forth the Applicants' contribution to the art and new claims 19-27 have been added to fully claim the present invention. These do not introduce new matter into the disclosure of the invention. The basis for the amendments to the claims can be found in paragraph 2, lines 1-4, paragraph 8, lines 1-5, paragraph 10, lines 1-2, paragraph 11, lines 1-8, paragraph 21, lines 12-16, paragraph 25, lines 111-12, and further in paragraph 37, lines 1-9, of the specification.

By way of review, the present invention relates to a targeted treatment for cancer with low systemic toxicity. The invention relies on the fact that tumor cells display elevated levels of the translation initiation factor, eIF4E. The eIF4E protein has been previously shown to be rate-limiting in cells for the initiation of protein synthesis. The eIF4E protein binds to the 5' m7pppG cap structure common to polyadenylated mRNAs and is part of a larger translation initiation complex (eIF4F), which is thought to bind to the 5' cap, unwind secondary structure in the 5' untranslated region (5' UTR) of mRNAs, and facilitate identification of the AUG initiation codon and 40S ribosomal recruitment and positioning. Messenger RNAs that contain sequences of long G/C rich 5' UTRs are poorly translated, including the vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2) mRNAs. In cells overexpressing eIF4E, VEGF and FGF2 mRNAs are efficiently translated.

The present invention provides for a chimeric DNA construct where, for example, the herpes simplex virus type-1 encoded thymidine kinase gene (HTK) is immediately downstream of FGF2 5' UTR sequence. The HTK gene is a widely used "suicide" gene, which can convert the prodrug ganciclovir (GCV) to a toxic metabolite in HTK expressing cells. The GCV metabolite acts as a chain terminator during DNA replication and consequently leads to HTK-expression and cell death. The HTK/GCV system is currently employed in a number of clinical trials. No trials currently use the compositions of the present invention.

The unique aspect of the inventors' FGF2 5' UTR/HTK (UTK) construct is that it can be efficiently translated only in eIF4E overexpressing cells and is poorly translated in normal, surrounding cells. As such, this regulation will confer tumor specific expression of the HTK gene and result in specific killing of tumor cells without undue collateral damage to normal cells in the body.

The novel aspect of this technology is the ability to specifically effect tumor cells -- *without relying upon any targeting of the material itself* -- while leaving normal cells relatively unscathed. This represents a *significant advance* for suicide gene therapy of solid tumors. Previously, tumor restricted expression of HTK or other suicide genes have relied on either localized administration of the HTK delivery vector (viral or DNA transfection) typically via intratumoral injection or through the use of tissue or tumor specific promoters. These techniques usually require specific knowledge of the cancer type and must be tailored almost individually, unlike the present invention that is applicable to most solid tumors.

The primary use for the constructs is for methods of treating tumors and similar cells overexpressing the eIF4E protein. This treatment may be used for both a primary tumor as well as secondary metastases.

Rejections Under 35 U.S.C. 112, First Paragraph

a. Written Description

The Examiner has rejected claims 10-18, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner has objected to the use of a large genus of untranslated sequences that inhibit translation in the absence of eIF4E and allow translation in the presence of eIF4E. The application specification describes this genus as being a sequence that is "a relatively long palindromic oligonucleotide sequence that is self-complementary."

The Examiner contends that the application provides only a description of the required function of the sequences, *i.e.*, the ability to inhibit translation in the absence of eIF4E and allow translation in the presence of eIF4E. However, the written description guidelines regarding genus/species situations only require a satisfactory disclosure of a

"representative number" of the species to show that the applicants had possession of the genus in view of the species disclosed. The Examiner alleges that the present specification fails to meet the requirements of section 112(1) because there is no written description of the structure of a species of the genus regarding a nucleic acid sequence that has the ability to inhibit translation in the absence of eIF4E. To support this rejection, the Examiner has cited *Fiers v. Sugano* and *Vas-Cath Inc. v. Mahurkar*. Applicants respectfully disagree with the Examiner.

Given that the Federal Circuit has affirmed that section 112(1) contains a written description requirement that is discrete from the enablement requirement, and that it can be unmet even when the enablement requirement is satisfied, it must be determined when the written description requirement is applicable. In *In re Smith*, 178 USPQ 620 (CCPA 1973), the court stated that the written description requirement is properly applied (a) under 35 USC 120, in determining whether a later filed claim is entitled to the filing date of the parent application, (b) in interference practice, in determining whether a specification supports a count, and (c) where a claim of an original application is subsequently amended. See MPEP 2163.03. The description requirement comes into play when a claim is added by an applicant at some stage after the original filing date and the claim differs in scope from the original claims.

The reason that the written description requirement only comes into play with respect to an amended claim is that an original claim is part of the specification. The claim in question constitutes its own description. However, when evaluating whether or not the written description requirement is met by the specification of an original application, in the context of the invention in a later presented claim, the court has simply evaluated the correspondence between the description of the invention in the specification and the description of the invention in the claims. Satisfaction of the description requirement insures that subject matter presented in the form of a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the prima facie date of invention can fairly be held to be the filing date of the application. Given that this is the role of the written description requirement, it is Applicants' position that the present specification more than adequately discloses and corresponds to the presently claimed subject matter.

In fact, while the specification of the present application does not contain the DNA sequence listings, the specification does provide for examples describing the use of 5' UTRs

from fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase. The sequences of such specific examples are very well-known in the art.

The 5' UTRs described offer a representative number of members of the genus showing the attributes or features as necessary for those skilled in the art. The Examiner has relied on *Fiers v. Sugano* to reject the present claims stating that "there is only a vague description of a nucleic acid sequence that would inhibit translation in the absence of eIF4E and allow translation in the presence of eIF4E."

Fiers relates to an interference proceeding in which the court found that the *Fiers* application did not meet the written description requirement with regard to the following count: "a DNA which consist essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide." *Fiers* at 1603. No such DNA sequence was disclosed in the *Fiers* application. The court held that the specification did not meet the written description requirement as conception of the claimed DNA did not occur upon conception of a method for obtaining it, but rather upon the inventor envisioning the detailed chemical structure of a gene so as to distinguish it from other materials and a method for obtaining the gene. However, in contrast to the count at issue in *Fiers*, the present application discloses and relies upon DNA sequences fully known in the art that are useful in the practice of the claimed invention, *i.e.*, the 5' UTRs from fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase. Thus, Applicants respectfully submitted that *Fiers* is not relevant to the facts of the present application.

As reported in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), claims reciting human cDNA encoding insulin were invalidated based on the failure of the specification to disclose "relevant structural or physical characteristics" of the human cDNA which amounted to "distinguishing characteristics" beyond the polypeptide encoded thereby. The Examiner is requested to note that the genes encoding the mRNA sequences of the present invention, including the 5' UTRs from fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase, have long been studied and their cloning and characterization were known in the art as of the effective filing date of the present claims.

References to these sequences can be found from NCBI (GeneBank), which lists the 5'UTR in addition to the coding sequence of most mRNAs. For the human *c-myc* the

GenBank accession number is M13930 (Bentley). For FGF-2 the GenBank accession number is NM002006 (Shibata).

Given the concededly high level of skill in the art, it would be a routine matter to one skilled in the art to isolate untranslated mRNA sequences which inhibit translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and which allow translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells using the techniques disclosed in previous papers. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. See, *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) and *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

The *Fiers* case represents the situation where an applicant wanted to patent a gene for a certain product but only had possession of the product without knowing the gene sequence. In the instant case, the present application is claiming an apparatus (a structure of DNA) as described by its relevant functional aspects combined with certain physical features. The sequences, as functionally described, provide adequate direction in the art of the human cDNA, which amounts to distinguishing characteristics.

The analysis of possession of the claimed invention depends on whether or not one skilled in the art would have understood the inventor to be in possession of the claimed invention at the time of filing even if every nuance of the claim is not explicitly described in the specification. What is conventional or well known to one skilled in the art need not be disclosed in detail. All that is necessary is a written description describing sufficient relevant identifying characteristics to show possession of the invention. The details of the specification are then viewed in light of the level of skill and knowledge in the art.

In the present case, representative specific 5' UTRs are described as those from fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase. Applicants may show evidence of possession of the entire genus by the relevant identifying characteristics of the group. These characteristics can be a complete or partial structure, physical and/or chemical properties, functional characteristics, correlation between structure and function, methods of making, or combinations of the above. *University of California; Revised Interim Guidelines for*

Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written Description" Requirement, 64 Fed. Reg. 71427 (Dec. 21, 1999) ("*Revised Interim Guidelines*").

The identifying characteristics in the present case are shown by the functional characteristics of the sequences. That is, the specific DNA sequences that are claimed in the present invention are those that, when transcribed, produce a messenger RNA sequence that comprises (a) a translatable sequence encoding a toxin, and (b) an untranslated sequence; wherein the untranslated sequence forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.

Applicants respectfully submit that one skilled in the art would find the specific functional characteristics of the claimed sequences an adequate representation of the genus. The claims of the present invention have now been amended to provide that the DNA, when transcribed, produce a messenger RNA sequence having a 5' untranslated sequence in front of the open reading frame, wherein the untranslated sequence inhibits translation of the toxin sequence under conditions which exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and wherein the untranslated sequence allows translation of the toxin sequence under conditions which exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells. Paragraph 11, lines 1-8.

To the extent that the written description requirement mandates that certain information must actually physically appear in the specification, the Examiner is requested to note that the complete disclosures of all references cited in the specification are all properly incorporated by reference into present specification. Thus, the Examiner is respectfully requested to identify the portions of these documents that are considered to be essential to the practice of the present invention and the Applicants will amended specification to include this material upon notification of otherwise allowable subject matter. The Examiner is particularly requested to note the incorporation by reference of the DeFatta dissertation. Therefore, the rejection of claims 10-18, based on the description requirement, is not appropriate and it is respectfully requested that it be withdrawn.

b. Enablement

The Examiner has also rejected claims 10-18 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art as to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner contends that although the claims are drawn to a DNA sequence, the intended use of the product is set forth in the claims is for administering to an animal therefore the claims broadly encompass gene therapy. While the Examiner has given a very thorough and detailed description of the reasons that the Examiner believes the disclosure does not meet the enablement requirement, Applicants respectfully disagree with the Examiner that the amount of experimentation required to make and use the present invention is undue.

The Examiner has evaluated the claims based on the scope of the vector, the scope of delivery, the scope of treatment, and the potential for ineffective *in vivo* responses as against the vector, cells or host. The Examiner must consider whether or not there is sufficient details on routes of administration of the polynucleotides and that sufficient expression of the gene can be achieved in the target cells upon delivery, that there is recognition in the art of a correlation between the animal model and human treatment, and that the expression of *c-myc* to the change within the cell correlates to the disease. These factors are determined by what is disclosed in terms of working examples in the specification, teachings of unpredictable parameters, what is known in the art, predictability of the art for the claim scope, correlation of working examples to the claimed invention, correlation of working examples in the prior art to the claimed invention, and correlation of animal models to the disease to be treated.

Applicants respectfully submit that the specification provides adequate direction to those skilled in the art and that the disclosure would not require undue experimentation. Furthermore, the claims have now been amended to more clearly set forth the invention as a selectively-regulatable DNA sequence, and not as a method of gene therapy. As fully described in section 5 of the examiner's office action, this determination can be made based on the factors to be considered as follows:

The nature of the invention. Applicants submit that the nature of the invention lends itself to the fact that the amount of experimentation required to perform the broadly claimed methods is not undue. This factor supports the Applicants' contention that the disclosure does not require undue experimentation since methods of gene therapy known as gene

directed enzyme prodrug therapy (GDEPT) were well-known in the art at the time of filing and the present invention utilizes a similar system. Koromilas AE (1992) *EMBO J.* **11**: 4153-4158; Johannes G (1999) *PNAS* **96**:13118-13123; McCormick F. (2001) *Nature Rev Cancer.* 1(2):130-41. Miller AD (1992). *Nature.* **357**: 455-460.

The breadth of the claims. Although the Examiner contends that the breadth of the claims is very broad in that the UTR can be any sequence having a relatively long palindromic oligonucleotide sequence that is self-complementary, the claim is not overly broad because Applicants have disclosed the concise mechanism of action that the claims of the present application require -- *i.e.,* that it requires an untranslated sequence that when placed in front of the open reading frame of the toxin gene, the untranslated sequence forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells -- and that mechanism defines the breadth of the materials that work.

Additionally, claims 17-19 require that the untranslated sequence has a stability ΔG of $\geq$ about 50 Kcal/Mol. Therefore, the claims are not as broad as indicated by the Examiner. They cover the true scope of the present invention and embodiments falling within those claims are easily determined by those skilled in the art by commonly known procedures.

The unpredictability of the art and the state of the prior art. The Examiner appears to have taken the stance that gene therapy as a whole is unpredictable as a mode of delivery in order to provide sufficient expression of genes sufficient to provide curative effects. The Examiner goes on to cite references regarding the efficacy of GDEPT therapy. The Examiner indicates that the main technical hurdle related to gene therapy is efficient targeting and delivery. The Examiner fails to appreciate that the present invention eliminates this hurdle by eliminating the necessity of the vector to target specific cells. In the present invention, the genes may target any cell within the subject but will show a therapeutic effect only in tumor cells due to the specificity of the presence of eIF4E. While the Examiner contends the results obtained in culture cannot be extrapolated to humans with a reasonable expectation of success, gene therapy has progressed dramatically in the past five years and many obstacles have been overcome. Applicants respectfully traverse this rejection in light of the showing of

working examples in the specification, the predictability of the art for the claim scope, the correlation of working examples of the claimed invention, the correlation of working examples in the prior art to the claimed invention, and the correlation of animal models to the disease. Applicants have provided sufficient detailed examples in the specification showing tumor ablation in mice injected with the present vectors. The U.S. Patent Office clearly does not require clinical data for gene therapy claims and that while gene therapy taken as a whole may be unpredictable, particular embodiments are patentable. Applicants have provided sufficient detail of particular patentable embodiments.

Working examples and guidance in the specification. The Examiner contends that in order to overcome the unpredictability of tumor treatment using a GDEPT system recognized in the art, the specification would have to show examples of the instant invention overcoming the recognized obstacles. The Examiner seems to indicate that it is necessary to show working examples comparing a construct that confers translationally controlled tumor specific toxin expression to a construct that confers transcriptional a controlled tumor specific toxin expression. Transcriptional and translational controls are different and there is little value to specifically comparing the systems as suggested by the Examiner. The present invention inherently is delivered to all cells within a subject.

Working examples and guidance in the specification. The Examiner contends that in order to overcome the unpredictability of tumor treatment using a GDEPT system recognized in the art, the specification would have to show examples of the instant invention overcoming the recognized obstacles. The Examiner seems to indicate that it is necessary to show working examples comparing a construct that confers translationally controlled tumor specific toxin expression to a construct that confers transcriptional a controlled tumor specific toxin expression. Transcriptional and translational controls are different and there is little value to specifically comparing the systems as suggested by the Examiner.

Applicants do not deny that there can be variation among species as to the level of expression of a particular gene that uses a particular expression promoter. However, the Examiner must keep in mind what Applicants are claiming. Applicants are not claiming a method of gene therapy where a specific tumor type must be targeted by the gene vector. Instead, Applicants' claims recite a DNA sequence that is capable of being transcribed to produce a messenger RNA sequence that comprises a translatable sequence encoding a toxin and furthermore comprising an untranslated sequence wherein the untranslated sequence

forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.

The Examiner has not provided convincing evidence as to why he believes that the results achieved using the art-recognized model disclosed in Applicants' specification cannot be correlated to efficacy in non-human primates or humans.

Quantity of experimentation. The Examiner contends that the quantity of experimentation is very large since, for example, experimentation is required to test the different toxins encompassed by the invention and different UTRs would have to be tested for their ability to control translation in the presence or absence of eIF4E. While it is true that the present invention would require experimentation to determine the proper schedules and drug combinations required, *etc.*, the level of experimentation required is not high relative to the level of skill in the art and complexity of the art. Applicants have provided working examples that show the use of different DNA sequences to control gene expression that constitutively expresses the toxin in all cell types. The determination of the appropriate vector and dosage of plasmid DNA or levels of expression that would be effective in treating tumors and the proper sequence for expressing the toxin in the tumor cells would necessarily be determined empirically and would be merely routine. Dosages of therapeutic agent effective in treating tumors are routinely extrapolated by methods known in the art.

While it might require considerable experimentation to arrive at the proper sequences for some toxin sequences, the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether undue experimentation is required to make and use the invention. An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. "The test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 USPQ2d at 1404 (CCPA 1076). The time and expense are merely factors in this consideration and are not the controlling factors.

The sequences that fall within the scope of the present claims are easily ascertained by any person skilled in the present art. The scope of the claims requires that the sequence is capable of being transcribed to produce a messenger RNA sequence that comprises a translatable sequence encoding a toxin and furthermore comprising an untranslated sequence wherein the untranslated sequence forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.

Therefore, sequence that does not produce a messenger RNA sequence that meets these criteria will inherently fall outside the scope of the present claims.

It is well within the scope of ability of one skilled in the art to test sequences of the present invention for the following reasons: (1) the amount of testing required is relatively small especially since most of the work can be done with tissue culture experiments as the proof of principle with the animal studies was already provided; (2) testing of any particular sequence in question would not require direction or guidance beyond that known in the art; (3) the current state of knowledge in the art and relative skill of those in the art is quite high; (4) well-known procedures exist for sequencing various DNA sequences capable of producing a messenger RNA sequences that comprises an untranslated palindromic sequences; and (5) determining whether or not a sequence falls within the scope of the claims is quite straightforward since all of the materials and methods that would be required to determine if a particular untranslated sequence forms a stable secondary structure that (i) substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.

Applicants submit herewith a Declaration from Robert Rhoads, Ph.D. demonstrating that one of ordinary skill in the art of molecular biology and medical science would know how to sequence various DNA and RNA sequences as well as how to test any particular sequence in order to determine whether or not the sequence produces a messenger RNA sequence that comprises (a) a translatable sequence encoding a toxin, and (b) an untranslated sequence; wherein the untranslated sequence forms a stable secondary structure that (i)

substantially inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.

Thus, is respectfully submitted that the present specification fully meets the requirements of 35 U.S.C. 112 and withdrawal of these rejections is respectfully requested.

Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 10-18 were rejected, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention.

The Examiner has objected to claim 10 for reciting the phrase "for administering to a mammal to inhibiting one or more metastatic tumors." Claim 10 has now been amended to read "to inhibit one or more." Furthermore, the Examiner has stated that it is unclear what exactly the DNA sequences inhibiting. Claim 10 has now been amended to more clearly set forth that the DNA sequence is for a regulated expression of a toxin.

The Examiner has objected to the phrase "untranslated region" in claims 11 and 15 as having insufficient antecedent basis and has indicated that this objection can be overcome by amending the phrase to read "untranslated sequence." This amendment has been made herein.

The Examiner has objected to claim 18 for reciting a phrase "a DNA sequence as recited in claim 1" when only claims 10-18 are present in the application. Claim 18 has now been amended to correct this typographical error to recite "as recited in claim 11."

Claim Rejections Under 35 U.S.C. 102

The Examiner has rejected claims 10-18 under 35 U.S.C. §102(a) as being anticipated by DeFatta. (Dissertation; cataloged March 20, 2001). Applicants herewith submit a Declaration under 37 CFR §1.132 traversing the rejection by showing that the inventorship of the present application is correct and that the reference discloses subject matter derived from the Applicants rather than invented solely by the author of the published article notwithstanding the authorship of the article, *i.e.*, that Applicants are the inventors of the

subject matter disclosed in the article and claimed in the application. Accordingly, §102(e) does not apply.

The Examiner has rejected claims 10, 13, and 14 under 35 U.S.C. §102(b) as being anticipated by Shimogori *et al.* (BBRC Vol. 223:544-548; 1996). The Shimogori *et al.* reference describes a specific sequence derived from the ornithine decarboxylase 5'UTR that specifically responds to the level of polyamines for translation, an example of auto-regulation of translation that does not pertain to the present invention's use of 5'UTR's that respond to levels of eIF4E.

Applicants submit that the 5'UTR described does not contain each and every limitation required by the present claims. Specifically, the Shimogori *et al.* reference does not provide for a 5'UTR sequence that when placed in front of the open reading frame, forms a stable secondary structure that (i) substantially inhibits translation of the open reading frame (toxin) sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and (ii) substantially allows translation of the open reading frame (toxin) sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.

While the Shimogori *et al.* reference describes a 188 bp sequence that does not encompass the full 5UTR of ODC which was found to respond to the eIF4E level (rev. in De Benedetti and Harris, 1999), and such sequence does not provide the appropriate level of stability and change in action in the presence ofeIF4E to selectively regulate translation of the open reading frame.

In light of this, it is submitted that the claims of the present application, as amended herein, are patentable over the references cited by the Examiner, and it is respectfully requested that the rejection under 35 U.S.C. 102(a) be withdrawn.

Claim Rejections Under 35 U.S.C. 103

On page 14, the Examiner states merely that "*claims [are] rejected under* 35 U.S.C. §103(a) as being unpatentable over Strathdee *et al.* (BioTechniques Vol. 28:210-214; 2000) and in view of Kevil *et al.* (Oncogene Vol. 11:2339-2348). Since the Examiner does not specify *which* claims are being rejected, Applicants are unable to fully respond to the

rejection under this paragraph but will assume that the Examiner is referring to all of the pending claims, 10-18.

Applicants note that the Examiner has attempted to combine the Strathdee *et al.* reference, describing various constructs of fusions between the TK open reading frame (ORF) and other reporter proteins to generate hybrid proteins, with the Kevil *et al.* reference, describing the 5'UTR of FGF-2 mRNA that has regulatory effects on the translation/expression of FGF-2 polypeptide. Applicants respectfully traverse this rejection.

In order to reject a patent application under section 103 using a combination of prior art, there must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill would make the combination. Applicants contend that there would have been no motivation to have combined the HTK gene with translational regulation of the FGF-2 5'UTR as the Examiner suggests. Specifically, the Examiner contends that the motivation to combine the references would have been "to further study the regulatory functions of the 5'UTR of FGF-2 taught by Kevil *et al.* by operably linking it to the selectable marker gene TK in a vector as taught by Strathdee *et al.*" First, a motivation to further study the functions of a product is not the correct standard. There would have been no motivation to combine the references to create the present invention since it would not have been known that such a construct could be used specifically for regulatory control within a tumor cell. The Examiner cannot make a *prima facie* case of obviousness if it would not have been known at the time the invention was made that the presence or absence of eIF4E would selectively regulate such a control region.

The Strathdee *et al.* reference refers to fusions of TK open reading frames (ORF), not translationally regulatory elements as in the present invention. It would not have been obvious in any way to combine the Strathdee *et al.* reference with the Kevil *et al.* reference since it would not have been obvious to one skilled in the art that the 5'UTR of of the present invention linked to TK would in fact confer translational regulation to the TK mRNA. It was not known at the time that such 5'UTRs could regulate translation of a different reporter mRNA and it was not known at the time that tumor cells particularly have high levels of eIF4E. Therefore, there would have been no motivation to link translational regulation of HTK by the 5'UTR's of the present invention.

Furthermore, at the time Kevil *et al.* was published it was not known that eIF4E was overexpressed in most tumors. As such, the benefit of regulating the translation of the HTK

mRNA to limit its expression in cancer cells overexpressing eIF4E could not be anticipated. Accordingly, it is submitted that the rejection under 35 U.S.C. 103 is not applicable to the claims of the present invention, as amended herein, and it is respectfully requested that it be withdrawn.

Based on the foregoing amendments and remarks, as well as the attached Declarations under 37 CFR 1.132, it is submitted that the present application is now in form for allowance. Therefore, early reconsideration and allowance of the claims, as currently pending, are solicited.

The Assistant Commissioner for Patents is authorized to charge any deficiency or credit any overpayment to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

DEBENEDETTI, Arrigo, *et al.*

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VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE SPECIFICATION:

IN THE CLAIMS:

Please amend the following claims as indicated:

10. (once amended) A DNA sequence [for administering to a mammal to inhibiting one or more metastatic tumors, said sequence] comprising a [constitutive] promoter operatively linked to a transcription sequence; wherein the transcription sequence, when transcribed, produces a messenger RNA sequence that comprises a translatable sequence encoding a toxin, and an untranslated sequence; wherein the untranslated sequence inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and wherein the untranslated sequence allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells [in the absence of eukaryotic initiation factor eIF4E, and wherein the untranslated sequence allows translation of the toxin sequence into a toxin in the presence of eukaryotic initiation factor eIF4E].

11. (once amended) A DNA sequence as recited in Claim 10, wherein the untranslated sequence allows translation of the toxin sequence under conditions which exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E at least 2-fold greater relative to normal cells [region comprises the 5' untranslated sequence of fibroblast growth factor-2; whereby, when placed in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the translation of the toxin, the toxin is translated to kill the tumor cell; and whereby the majority of non-tumor cells in the mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells].

12. (once amended) A DNA sequence as recited in Claim 10, wherein the untranslated sequence [region] comprises the 5' untranslated sequence selected from the group consisting of fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase[; whereby, in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the

translation of the toxin, the toxin is translated to kill the tumor cell; and whereby the majority of non-tumor cells in the mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells].

14. (once amended) A DNA sequence as recited in Claim 13, wherein the encoded conditional toxin is a herpes thymidine kinase[; and wherein the method additionally comprises administering an effective amount of ganciclovir to the mammal; whereby, in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the translation of herpes thymidine kinase, and in which ganciclovir is taken up by the cell, the translated herpes thymidine kinase in the cell phosphorylates the ganciclovir, allowing the phosphorylated ganciclovir to kill the tumor cell; and whereby the majority of non-tumor cells in the mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells].

15. (once amended) A DNA sequence as recited in Claim 14, wherein the untranslated sequence [region] comprises the 5' untranslated sequence of fibroblast growth factor-2.

16. (once amended) A DNA sequence as recited in Claim 14, wherein the untranslated sequence [region] comprises the 5' untranslated sequence selected from the group consisting of proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase.

17. (once amended) A DNA sequence as recited in Claim 10, wherein the untranslated sequence comprises mRNA with a [hairpin] secondary structure conformation having a stability of $\Delta G \geq$ about 50 Kcal/Mol.

18. (once amended) A DNA sequence as recited in Claim [1, wherein the metastatic tumor is associated with a mammalian cancer selected from the group consisting of bladder, breast, cervical, colon, prostrate, and head and neck] 17, wherein the untranslated sequence comprises a G/C- rich 5'UTR sequence.

Please add the following new claims:

IN THE CLAIMS:

Please amend the following claims as indicated:

10. (once amended) A DNA sequence [for administering to a mammal to inhibiting one or more metastatic tumors, said sequence] comprising a [constitutive] promoter operatively linked to a transcription sequence; wherein the transcription sequence, when transcribed, produces a messenger RNA sequence that comprises a translatable sequence encoding a toxin, and an untranslated sequence; wherein the untranslated sequence inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and wherein the untranslated sequence allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells [in the absence of eukaryotic initiation factor eIF4E, and wherein the untranslated sequence allows translation of the toxin sequence into a toxin in the presence of eukaryotic initiation factor eIF4E.]

11. (once amended) A DNA sequence as recited in Claim 10, wherein the untranslated sequence allows translation of the toxin sequence under conditions which exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E at least 2-fold greater relative to normal cells [region comprises the 5' untranslated sequence of fibroblast growth factor-2; whereby, when placed in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the translation of the toxin, the toxin is translated to kill the tumor cell; and whereby the majority of non-tumor cells in the mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells].

12. (once amended) A DNA sequence as recited in Claim 10, wherein the untranslated sequence [region] comprises the 5' untranslated sequence selected from the group consisting of fibroblast growth factor-2, cyclin D1, proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase[; whereby, in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the translation of the toxin, the toxin is translated to kill the tumor cell; and whereby the majority of non-tumor cells in the mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells].

13. (once amended) A DNA sequence as recited in Claim 10, wherein the encoded toxin is a conditional toxin.

14. (once amended) A DNA sequence as recited in Claim 13, wherein the encoded conditional toxin is a herpes thymidine kinase[; and wherein the method additionally comprises administering an effective amount of ganciclovir to the mammal; whereby, in a metastatic tumor cell in which the presence of eukaryotic initiation factor eIF4E allows the translation of herpes thymidine kinase, and in which ganciclovir is taken up by the cell, the translated herpes thymidine kinase in the cell phosphorylates the ganciclovir, allowing the phosphorylated ganciclovir to kill the tumor cell; and whereby the majority of non-tumor cells in the mammal are not killed due to the low levels of eukaryotic initiation factor eIF4E typically present in non-tumor cells].

15. (once amended) A DNA sequence as recited in Claim 14, wherein the untranslated sequence [region] comprises the 5' untranslated sequence of fibroblast growth factor-2.

16. (once amended) A DNA sequence as recited in Claim 14, wherein the untranslated sequence [region] comprises the 5' untranslated sequence selected from the group consisting of proto-oncogene *c-myc*, vascular endothelial growth factor, and ornithine decarboxylase.

17. (once amended) A DNA sequence as recited in Claim 10, wherein the untranslated sequence comprises mRNA with a [hairpin] secondary structure conformation having a stability of $\Delta G \geq$ about 50 Kcal/Mol.

18. (once amended) A DNA sequence as recited in Claim [1, wherein the metastatic tumor is associated with a mammalian cancer selected from the group consisting of bladder, breast, cervical, colon, prostrate, and head and neck] 17, wherein the untranslated sequence comprises a G/C- rich 5'UTR sequence.

Please add the following new claims:

19. (new) A DNA sequence as recited in Claim 18, wherein the untranslated sequence comprises mRNA with at least one substantially palindromic oligonucleotide sequence that is self-complimentary.

20. (new) A DNA sequence as recited in Claim 10, wherein the conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells are those that exist in metastatic tumor cells.

20. (new) A messenger RNA sequence that comprises a translatable sequence encoding a toxin, and an untranslated sequence; wherein the untranslated sequence comprises an mRNA sequence with a secondary structure conformation having a stability $\Delta G \geq$ about 50 Kcal/Mol and wherein the untranslated sequence inhibits translation of the toxin sequence under conditions that exist within normal mammalian cells that do not overexpress eukaryotic initiation factor eIF4E and wherein the untranslated sequence allows translation of the toxin sequence under conditions that exist within mammalian cells that overexpress eukaryotic initiation factor eIF4E relative to normal cells.

21. (new) A vector comprising the DNA sequence of claim 10.

22. (new) The vector of claim 21, wherein the vector is a viral vector.

23. (new) The vector of claim 22, wherein the vector is a non-viral vector.

24. (new) The vector of claim 23, wherein the vector is a BK vector.

25. (new) A pharmaceutical composition comprising a therapeutically effective amount of the vector of claim 21 and a carrier.

26. (new) The pharmaceutical composition of claim 25 wherein the carrier is a liposomal complex.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Box Amendment Fee, The Assistant Commissioner for Patents, Washington, D.C., 20231, this 24th day of October, 2002.

Joyce O. Fields

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